PATENT

Attorney Docket No. 11160-002

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

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| Inventor: | Kivlighn et al. | ) | |
| | | ) | Group Art Unit: 1617 |
| Serial No.: | 09/892,505 | ) | |
| | | ) | Examiner: Kantamneni, Shobha |
| Filed: | June 28, 2001 | ) | |

Title: Treatment For Cardiovascular Disease

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Sir:

APPELLANT'S REPLY BRIEF UNDER 37 CFR § 41.41

This Reply Brief is filed following the Examiner's Answer issued in the above-captioned application on November 5, 2008. This is not a substitute Appeal Brief. Any ground for rejection in Examiner's Answer that is not refuted herein is considered by Appellant to have been sufficiently argued in the Appeal Brief, such that no further comment is needed herein. Arguments herein focus on certain factual errors in the Examiner's answer.

ARGUMENT

a. Remarks in Rebuttal of the 35 USC § 103(a) rejection of claims 16-17 in view of Maeda et al. in view of Nakamoto et al. and further in view of Applicants' Admission

The Examiner states that Maeda et al. discloses a method of treating hypertension comprising administering to a patient in need thereof a therapeutically effective amount of a xanthine oxidase inhibitor 4-amino-6-hydroxypyrazolol [3,4-d]pyrimidine (AHPP). However, what is relevant to this analysis is whether Maeda et al. suggests that uric acid should be controlled as a treatment for hypertension, and/or whether lowering uric acid to specified levels would be expected to treat hypertension. As explained below, Applicants respectfully assert that the Maeda et al. reference lacks any such suggestion.

Applicants' provided evidence in the main brief demonstrating that Maeda et al. tested AHPP on an animal model (the spontaneous hypertensive rat, or SHR) that has been shown to be nonresponsive to lowering and increasing uric acid levels. In other words, Applicants' evidence demonstrates that any anti-hypertensive effect of AHPP did not involve a lowering of uric acid. Rather, hypertension in the SHR is caused by oxidative stress (as shown in the previously cited Rodriguez-Iturbe Declaration). Accordingly, Maeda et al. lacks a suggestion to target the lowering of uric acid in the treatment of hypertension.

The Examiner states that Maeda et al. teach that AHPP showed a lowering of uric acid in a dose-dependent manner. The data to which the Examiner refers only relates to an in vitro assay where uric acid was used as a marker to determine whether AHPP inhibited xanthine oxidase. Nowhere does Maeda et al. teach or contemplate that uric acid itself should be lowered as a means to control hypertension. Maeda et al. provide no teaching concerning dosing of AHPP to achieve a certain physiological uric acid level, much less the specific, physiological ranges of uric acid that Applicants have discovered to be most therapeutically effective.

The Examiner states that Nakamoto et al. teaches that compounds that lower uric acid are effective in treating hypertension. Applicants respectfully disagree that Nakamoto actually

teaches this. Nakamoto made a confusing statement concerning uric acid that lacks support by any scientific data or journal citations. Applicants provided unrefuted evidence in their main brief demonstrating that those skilled in the art declared that uric acid was irrelevant to hypertension several years after, and in contradiction to Nakamoto et al.'s unsupported statement. Applicants have also provided evidence that Nakamoto et al.'s unsupported statement was not considered a valid medical/scientific statement concerning uric acid and hypertension by those skilled in the art. This is further supported by the fact that Nakamoto et al. never followed up on the alleged proposition that uric acid had an effect on hypertension. It has not been refuted by the Examiner that it was the Applicants who first discovered that uric acid possesses a causative role in hypertension. To reiterate the statement of the Expert Dr. Weir provided in Applicants' main brief: "Dr Johnson is the first to specifically investigate if uric acid might be a cause of hypertension and to provide direct evidence of such."

The Examiner states that it would have been obvious to a person of ordinary skill in the art to determine the optimal parameters such as effective amounts of xanthine oxidase inhibitor need to achieve desired results. Applicants respectfully disagree. As of the time of filing the present application, the overwhelming conclusion by those in the art was that uric acid was not relevant to hypertension. It was only after Applicants developed a suitable model to test whether uric acid played a role in hypertension that they discovered that increased uric acid levels did increase hypertension. Applicants' work is the first scientific demonstration that increases in uric acid increase hypertension. Moreover, it was only after Applicants' discovery and the teachings of the present application that one skilled in the art could then determine what specific concentrations of uric acid should be targeted for therapeutically efficacy.

The Examiner states that "Applicant acknowledges that uric acid was known as a possible risk factor for hypertension." Applicants' respectfully assert that this statement has been taken out of context and misapplied. Firstly, this statement did not mean that uric acid was believed by those skilled in the art to cause hypertension, quite the contrary. When the complete passage is considered, the clear meaning of the statement is easily apprehended:

> "While the association of uric acid with hypertension has been known since our early work, this certainly did not prove that uric acid is a cause of hypertension. Indeed, the scientific community (as exemplified by guidelines published by the major societies on hypertension and cardiovascular disease) have not considered uric acid as having a causal role in hypertension."

Applicants have provided a thorough explanation, supported by evidence, showing that the statement was talking about association/correlation of uric acid not causation. As stated, it is well known that association does not prove cause and effect. To provide another illustrative example, there may be a strong association between beer drinking in adult men and watching the superbowl, but that does not mean that watching the superbowl causes men to drink beer, but rather it is likely that the type of men who like to watch the superbowl are also the type of men that like beer. As Applicants have already extensively detailed, the association of uric acid with hypertension, while well known, was thought to be due to the fact that the type of people who develop hypertension are also the same type of individual who is likely to get gout (such as obese individuals with prediabetes).

Applicants respectfully solicit the Board to consider the clear context and intent of the cited statement by Applicants. The Examiner has sought to use this statement as an admission by the Applicants that those skilled in the art would believe that uric acid levels can be controlled as a means to control hypertension. Applicants respectfully assert that this is in error.

The foregoing notwithstanding, the point becomes moot in light of the fact that the notion of uric acid being a possible risk factor, or most importantly, a causal factor, was overwhelmingly dispelled by experts in the field as of the time of the invention and filing of the present application. Applicants have thoroughly demonstrated this fact with copious evidence provided in Applicants' main brief (see Declarations from Drs. Rodriguez-Iturbe, Bakris, Johnson and Weir).

As of the time of filing the present application, the prior art when viewed as a whole demonstrates that there was no motivation in the art to attempt to control hypertension by controlling uric acid levels. Furthermore, Applicants' evidence shows that at the time of filing the present application, those skilled in the art did not believe that uric acid was relevant to hypertension, much less that increased uric acid levels could be causative. It is noted that the Examiner provides no scientific evidence refuting Applicants' proffered evidence on these salient points. Moreover, without the knowledge of Applicants' discovery, the skilled artisan would have had no reason to seek to discover ranges of uric acid levels that would be most therapeutically effective in controlling hypertension. Thus, when the prior art is viewed as a whole, the differences between the prior art and the claimed invention are not insubstantial. The claimed invention should not be considered obvious.

b. Remarks in Rebuttal of the 35 USC § 103(a) rejection of claim 18 in view of Baldwin (US 4,058,614), in view of Baldwin et al. (US 4,032,522)

The Examiner states that it "would have been obvious to a person of ordinary skill in the art at the time of invention to administer allopurinol in the method of treating hypertension because 1) Baldwin '614 teaches that xanthine oxidase inhibitors are useful in treating hypertension and 2) Baldwin et al. '522 teach that allopurinol acts as a specific inhibitor of the enzyme xanthine oxidase. In response, Applicants assert that, as a basic premise, nowhere do either Baldwin references recognize, teach or suggest that there is any connection between inhibition of xanthine oxidase and hypertension, much less a connection between uric acid levels and hypertension. Moreover, nowhere do the cited references suggest that allopurinol can be administered to treat hypertension.

The Baldwin '614 reference teaches a broad and diverse group of substituted imidazole compounds and states that the compounds "are active as xanthine oxidase inhibitors or in treating hypertension." (emphasis added). Indeed, if the agents had both activities, then the patent application would have said that the compounds have both xanthine oxidase and antihypertensive activity, but throughout the application the authors always use the word "or" which by definition

means one or the other (but not both). Furthermore, allopurinol is not a substituted imidazole and Baldwin '614 never suggests that it is xanthine oxidase blockade that is responsible for lowering blood pressure.

Baldwin '522 teaches that the imidazole compounds should be separated in into two different groups: a group of trifluormethylimidazole compounds that function as anti-hypertensives (column 6, line 7) and a separate group that function for the treatment of gout (xanthine oxidase inhibition, column 4, line 23). Thus, a reasonable conclusion from the Baldwin references is that anti-hypertensive activity is distinct from xanthine oxidase inhibition.

Thus, it can be reasonably concluded that one skilled in the art would not be led by the cited Baldwin references to target uric acid levels to control hypertension, much less to target the specific uric acid levels that Applicants have found to be particularly therapeutic effective, and/or treat hypertension with allopurinol. Further, the Baldwin references provide no basis to assert that there was an expectation of success of controlling hypertension by lowering uric acid. Applicants have provided evidence that those skilled in the art at the time of filing the present application believed that hypertension could not be successfully treated by controlling uric acid levels (which has not been countered by any scientific evidence offered by the Examiner). In view of the foregoing, claim 18 should be viewed as nonobvious over the cited Baldwin references.

c. Other considerations:

The Applicants therefore submit that the use of xanthine oxidase inhibitors, and in particular allopurinol, as a means to treat hypertension was not obvious to someone skilled in the art. Indeed, if it were obvious, then how can the Examiner explain the following:

1. If an elevated uric acid is considered a causative risk factor for hypertension, then why is not lowering uric acid suggested by the state-of-the-art paper on hypertension management, that being the report of the The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure:

the JNC 7 report (JAMA2003; 289:2560-2572) (see Declarations of Drs. Weir and Bakris) and why is it not at least listed as a major risk factor?

2. Hypertension is not a minor disease; currently over 1 billion people suffer from this condition. If xanthine oxidase inhibitors, and in particular allopurinol (available since the 1960s) was thought to be effective in treating hypertension, then why have we not seen studies showing efficacy and why were xanthine oxidase inhibitors, or allopurinol, not introduced as a treatment, prior to the filing of the present application?

3. If Nakamoto in 1991 teaches that uric acid agents are known to treat hypertension, why are there no references to Nakamoto's work for this proposition?

4. If serum uric acid was thought to play a causative role in lowering uric acid at the time of the invention, why did the Framingham Heart Study group after having previously declared in 1999 that uric acid does not play a causative role in hypertension, reverse their position in 2005 crediting the inventors' work?

Applicants urge the Board to consider that the real reason that allopurinol and xanthine oxidase inhibitors have not been used to treat hypertension is because uric acid has not been considered a causative risk factor for hypertension. The studies led by Johnson et al have led to a reappraisal and have generated the first convincing data (Mazzali et al, Hypertension, 2001; 38: 1101-1106). Applicants assert that the pending rejections of claims 16-18 as being obvious under 35 U.S.C. (103a) are not supportable. Treating hypertension with either allopurinol or xanthine oxidase inhibitors and in particular targeting levels to a uric acid of 4-6 mg/dl was not obvious to the ordinarily skilled artisan at the time the present application was filed.

Respectfully submitted,

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